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Effect of Anesthetics on the Pituitary-Adrenocortical System of the Rat

Takaaki MITAMURA *

Department of Physiology, Nagasaki University School of Medicine, Nagasaki, Japan

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The effect of various anesthetics on the pituitary-adrenocortical system was studied in rats, using the depletion of adrenal ascorbic acid as an index of adrenal-cortical activity. The anesthetics applied were Evipan-sodium, ether, urethane, morphine and sodium pentobarbital. Anesthetization with ether, urethane and morphine (10 mg per 100 g body weight) induced a remarkable adrenal ascorbic acid depletion in rats. Ascorbic acid depletion in the adrenal after application of Evipan-sodium or morphine (2 mg per 100 g body weight) was mild, and no definite change in adrenal ascorbic acid concentration was produced by sodium pentobarbital anesthesia. In hypophysectomized rats anesthetization did not produce adrenal ascorbic acid depletion.

Previous studies in our laboratory indicate that the rate of 17-hydroxycorticosteroid secretion into adrenal vein blood of unanesthetized dogs is increasd by ether anesthesia[8] and morphine administration.[9]

The present investigation was designed to study extensively the effects of anesthetics on the pituitary-adrenal system in rats, using the adrenal ascorbic acid depletion as an index of adrenal-cortical activity.

METHODS

Adult male albino rats of an inbred strain, 142 in total, were used for this study.

The anesthetics given were Evipan-sodium (Bayer), ether, urethane, morphine hydrochloride and sodium pentobarbital (Nembutal, Abbott). All these anesthetics, except for ether, were dissolved in 1 cc saline solution per 100 g body weight and were then injected subcutaneously. For controls of animals given ether, non-treated rats were used. In cases of other anesthetics, control rats injected with 1 cc of saline solution per 100 g body weight two hours prior to sacrificing were run simultaneously with each experimental group. However, a fall in adrenal ascorbic acid concentration was found to be induced by an injection of saline solution alone. In order to obviate this phenomenon, all rats used in this study, except for etherization experiments, were accustomed to injection by the administration of saline solution twice daily for a week as described by HOLZBAUER and VOGT.[4]

Hypophysectomy was carried out through the parapharyngeal approach under ether anesthesia three days prior to the experiment.

The rats were killed by a blow on the head two hours after the administration of anesthetics or saline and both adrenals were then quickly removed. The ascorbic

* 三田村孝朗

acid estimations were made on trichloroacetic acid extracts of the adrenal glands by the method of ROE and KUETHER.[7] The data are expressed as mg per 100 g fresh adrenal.

RESULTS

Evipan-sodium anesthesia

Evipan-sodium (15 mg per 100 g body weight) was injected twice at an interval of one hour in order to maintain deep anesthesia for two hours. Adrenal ascobic acid responses to this anesthetic are shown in Table 1.

TABLE 1.
The Effect of Evipan-Sodium Anesthesia on Adrenal Ascorbic Acid Concentration in Rats

Group	No. of rats	Treatment	Adrenal ascorbic acid conc. (mg/100 g) Mean ± S.E.*	P compared with group a
a	5	Control-Saline	454 ± 7.5	
b	7	Evipan-sodium	349 ± 10.8	< 0.01
a	6	Hypophysectomized Control-Saline	475 ± 10.6	
b	8	Hypophysectomized Evipan-sodium	449 ± 8.3	> 0.05

* Standard error of the mean

It was found that adrenal ascorbic acid concentration of rats anesthetized with Evipan-sodium was lower than that of control animals. The difference in estimates between these two groups was statistically significant. The adrenal ascorbic acid response to this anesthetic was proved to be completely abolished by hypophysectomy.

Urethane anesthesia

Urethane (175 mg per 100 g body weight) was given subcutaneously. The results are presented in Table 2.

TABLE 2.
The Effect of Urethane Anesthesia on Adrenal Ascorbic Acid Concentration in Rats

Group	No. of rats	Treatment	Adrenal ascorbic acid conc. (mg/100 g) Mean ± S.E.	P compared with group a
a	6	Control-Saline	447 ± 8.4	
b	10	Urethane	241 ± 7.3	<0.001
a	5	Hypophysectomized Control-Saline	424 ± 8.9	
b	7	Hypophysectomized Urethane	420 ± 7.5	>0.70

Urethane anesthesia produced a remarkable drop in adrenal ascorbic acid concentration in normal rats, whereas in hypophysectomized rats no adrenal ascorbic acid response to this anesthetic was observed.

Ether anesthesia

The rats were placed in a large glass vessel with a vent and were then etherized. They were then taken out of the vessel. A piece of absorbent cotton, on which ether was dropped continually, was placed under the rat's nose. In this way deep anesthesia was maintained for two hours. The results are summarized in Table 3.

TABLE 3.
The Effect of Ether Anesthesia on Adrenal Ascorbic Acid Concentration in Rats

Group	No. of rats	Treatment	Adrenal ascorbic acid conc. (mg/100 g) Mean ± S.E.	P compared with group a
a	10	Control	452 ± 10.1	
b	10	Ether	243 ± 7.1	<0.001
a	5	Hypophysectomized Control	456 ± 6.7	
b	8	Hypophysectomized Ether	465 ± 10.5	>0.50

Ether anesthesia produced a significant fall in adrenal ascorbic acid in normal rats. By the same procedure no lowering of adrenal ascorbic acid concentration was induced in hypophysectomized rats.

Morphine anesthesia

Morphine hydrochloride (2 mg or 10 mg per 100 g body weight) was injected subcutaneously. The results are presented in Table 4.

TABLE 4.
The Effect of Morphine on Adrenal Ascorbic Acid Concentration in Rats

Group	No. of rats	Treatment	Adrenal ascorbic acid conc. (mg/100 g) Mean ± S.E.	P compared with group a
a	5	Control-Saline	438 ± 7.6	
b	10	Morphine 2 mg	353 ± 9.3	<0.001
a	5	Control-Saline	445 ± 11.3	
b	7	Morphine 10 mg	291 ± 10.1	<0.001
a	5	Hypophysectomized Control-Saline	419 ± 7.9	
b	7	Hypophysectomized Morphine 10 mg	421 ± 7.7	>0.80

Marked depletion of adrenal ascorbic acid was induced by morphine. This lowering of concentration was not produced in hypophysectomized rats even by the administration of 10 mg morphine per 100 g body weight.

Sodium pentobarbital anesthesia

Five mg sodium pentobarbital per 100 g body weight was injected subcutaneously. The results are presented in Table 5. No definite alteration of adrenal ascorbic acid concentration was demonstrated.

TABLE 5.
The Effect of Sodium Pentobarbital Anesthesia on Adrenal Ascorbic Acid Concentration in Rats

Group	No. of rats	Treatment	Adrenal ascorbic acid conc. (mg/100 g) Mean ± S.E.	P compared with group a
a	6	Control-Saline	416 ± 8.6	
b	10	Sodium pentobarbital	422 ± 6.4	>0.50

DISCUSSION

These data indicate that some anesthetics affect the pituitary-adrenocortical system of rats as stressing agents.

Ether, urethane and morphine (10 mg per 100 g body weight) anesthesia produced a remarkable adrenal ascorbic acid depletion. The magnitude of reduction in adrenal ascorbic acid caused by Evipan-sodium and morphine (2 mg per 100 g body weight) was relatively small and no adrenal ascorbic acid depletion was produced by sodium pentobarbital anesthesia.

Adrenal ascorbic acid depletion caused by ether anesthesia was demonstrated in a histological study by LAUBER, DUMKE and PATZSCHKE.[5] BOWMAN and MUNTWYLER,[1] in a study in which they employed a chemical method, observed a decrease in adrenal ascorbic acid concentration caused by ether anesthesia. As to the effect of urethane anesthesia on the adrenal ascorbic acid concentration, it has been shown by VOGT[10] that 1.5 g urethane per kg body weight acted as a strong stressing agent in normal rats and decreased their adrenal ascorbic acid by about 50%. The depletion of adrenal ascorbic acid induced by morphine administration has been reported by NASMYTH,[6] BRIGGS and MUNSON,[2] GEORGE and WAY.[3] That Evipan anesthesia produces a relatively small decrease in adrenal ascorbic acid concentration was also reported by LAUBER, DUMKE and PATZSCHKE.[5] The above observations are confirmed by the present study.

The depletion of adrenal ascorbic acid caused by ether, urethane, morphine and Evipan-sodium in all probability occurred in association with the discharge of ACTH from the anterior pituitary. This conclusion is established in the present study by the finding that no change in adrenal ascorbic acid concentration was produced by the above anesthetics in hypophysectomized rats.

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